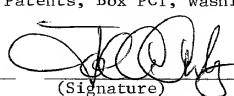



404 Rec'd PCT/PTO 25 AUG 1998

US

Annex US.II, page 1

FORM PTO-1500 (REV. 12-97)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER TORO 0101 PUS	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
				09/125747	
INTERNATIONAL APPLICATION NO. PCT/FR97/00334		INTERNATIONAL FILING DATE 25 Feb. 1997 (25.02.97)		PRIORITY DATE CLAIMED 26 Feb. 1996 (26.02.96)	
TITLE OF INVENTION ANTI-HELICOBACTER VACCINE COMPLEX					
APPLICANT(S) FOR DO/EO/US TOROSSIAN, Fernand, Narbey					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:					
<p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</p> <p>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <p style="margin-left: 20px;">a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</p> <p style="margin-left: 20px;">b. <input type="checkbox"/> has been transmitted by the International Bureau.</p> <p style="margin-left: 20px;">c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</p> <p>6. <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</p> <p>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <p style="margin-left: 20px;">a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</p> <p style="margin-left: 20px;">b. <input type="checkbox"/> have been transmitted by the International Bureau.</p> <p style="margin-left: 20px;">c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</p> <p style="margin-left: 20px;">d. <input type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input checked="" type="checkbox"/> A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>					
Items 11. to 16. below concern document(s) or information included:					
<p>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input type="checkbox"/> A FIRST preliminary amendment.</p> <p style="margin-left: 20px;"><input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>14. <input type="checkbox"/> A substitute specification.</p> <p>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>16. <input type="checkbox"/> Other items or information:</p>					
<p>I hereby certify that this correspondence is being deposited with the United States Postal Service as "Express Mail" under Label No. EG152829816US in an envelope addressed to: Asst. Commissioner for Patents, Box PCT, Washington, D.C. 20231 on:</p> <p style="text-align: center;">8/25/98</p> <p>(Date of Deposit)</p>					
		By: John A. Artz		 (Signature)	
		(Attorney)			

300 Rec'd PCT/PTO 25 AUG 1998

U.S. APPLICATION NO. (if known see 37 CFR 1.5)		INTERNATIONAL APPLICATION NO. PCT/FR97/00334		ATTORNEY'S DOCKET NUMBER TORO 0101 PUS	
17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)): Search Report has been prepared by the EPO or JPO \$930.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) \$720.00 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) \$790.00 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$1070.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) \$98.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS PTO USE ONLY	
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)). <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30				\$ 930.00	
				\$ 130.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	8 - 20 =	-0-	x \$22.00	\$	-0-
Independent claims	3 - 3 =	-0-	x \$82.00	\$	-0-
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ \$270.00	\$ 270.00
TOTAL OF ABOVE CALCULATIONS =				\$ 1,330.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				\$	+
SUBTOTAL =				\$ 665.00	
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)). <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30				\$ 130.00	
TOTAL NATIONAL FEE =				\$ 795.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$ -0-	
TOTAL FEES ENCLOSED =				\$ 795.00	
				Amount to be refunded:	\$
				charged:	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>795.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>50-0476</u> . A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: John A. Artz LYON & ARTZ PLC 28333 Telegraph Road, Suite 250 Southfield, MI 48034					
				 SIGNATURE John A. Artz NAME 25,824 REGISTRATION NUMBER	

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) & 1.27(b))--INDEPENDENT INVENTOR

Docket Number (Optional)
TORO_0101_PUS

Applicant or Patentee: TOROSSIAN, Fernand, Narbey
09/125747

Serial or Patent No.: PCT/FR97/00334
300 Rec'd PCT/PTO 25 AUG 1998

Filed or Issued: 25 Feb. 1997 (25.02.97)

Title: Anti-Helicobacter vaccine complex

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees to the Patent and Trademark Office described in:

- ☐ the specification filed herewith with title as listed above.
- ☒ the application identified above.
- ☐ the patent identified above.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

- ☒ No such person, concern, or organization exists.
- ☐ Each such person, concern or organization is listed below.

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Fernand Narbey TOROSSIAN

NAME OF INVENTOR

Signature of inventor

Date July 17, 1998

NAME OF INVENTOR

Signature of inventor

Date

NAME OF INVENTOR

Signature of inventor

Date

WO 97/30716

The present invention relates to a therapeutic and preventive anti-bacterial vaccine complex which possesses a vaccinating power linked to the presence of specific antigens against *Helicobacter pylori* (previously
5 called *Campylobacter pylori*), *Helicobacter hepaticus*, *Helicobacter coronari*, and nonspecific antigens providing immunomodulation.

[MARSHALL B.J., WARREN Jr., Unidentified curved bacilli in the stomach of patients with gastritis and
10 peptic ulceration *Lancet* 1984: i:1311-4)].

[MÉGRAUD F., *Helicobacter pylori*, the most important bacterium among the mucus bacteria, *La lettre de l'infectiologue* 1993; 8 (suppl. 4): 151-9].

It is well known, in bacteriology, that the
15 surface antigens of the walls, membranes or capsules (combined or free in soluble form in the culture medium) are of a glycoprotein, polypeptide or polysaccharide nature.

Vaccines combining associative factors, such as
20 membrane proteoglycan or polysaccharide substances, extracted from pathogenic microbes, with ribonucleic acid of ribosomal origin (RNA) can be used in the production of acellular vaccines (cf. *Inf. and Immunity*, 1, 574-82, 1970 and PCT WO 94/22462).

25 These vaccines use specific antigens corresponding to specifically determined microbial diseases.

However, the antigenicity is essentially linked to the level of RNA (of the ribosomes in particular) in microbial cells, inter alia. Immunocompetent cells (ICC)

directly use these RNAs as active carriers.

To produce the complex of the invention, with the Helicobacter bacterial serotype antigen, we coupled preferably by means of covalent bonds, RNA, preferably of
5 ribosomal origin, with an amino acid sequence of glycoprotein nature, preferably present in type III collagen. In humans, collagen represents approximately a third of the proteins in the body. The type III was chosen for its amino acid sequence and its presence in
10 the dermis, the vascular wall and the digestive epithelial mucous membranes.

In our complex, we have used, as stabilizer, cell membrane fractions derived from the same microbes as those which served for the production of the ribosomal
15 RNA. These membrane fractions contain all of the peptidoglycan substances and are known, in addition, as immunity adjuvants.

It is, in addition to Helicobacter pylori, hepaticus and coronari, useful to have - glucopolysaccharide or proteoglycan - membrane fractions derived
20 from various microbial organisms which have served to provide the RNA by extraction of their ribosomes, which microbes are known for their immunogenesis (recruitment of macrophages, activation of T lymphocytes, potentiation
25 of the synthesis of immunoglobulins, secretory IgA's in particular (11 S), increase in phagocytosis and stimulation of dependent T cells and the like).

This was thus thought of because, in the precise case of the pathogenesis induced by Helicobacter pylori,

hepaticus or helmannii, coronari, the body must produce, in addition to the specific humoral immune response, a cellular response in order to make up for the inefficacy of the antibodies in protecting the individual.,

5 It is known that cell-mediated response does not give rise to the production of antibodies, but only to the generation of sensitized lymphoid cells specific for the antigen involved.

10 The T lymphocytes act by themselves and/or through the cytokines, and either an inflammatory type response or a cytotoxic response is observed.

15 The pathogenic power of Helicobacter lies in its ability to colonize the gastric mucous membrane, to survive in the gastric juice and to multiply therein in spite of the host's immune response, and to generate lesions which are sometimes irreversible (adenocarcinoma, gastric lymphoma or MALT "mucous associated lymphoid tissue" lymphomas),

20 [PARSONNET J: Helicobacter pylori and gastric cancer. Gastroenterol Clin North Am 1993, 22:89-104.

25 WORTHERSPOON A.C., DOGLIONI C., DISS T. C. et al.: Regression of primary low-grade B-cell gastric lymphoma of mucosa associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet 1993; 342:575-7.

 MOHANDAS, Helicobacter pylori and lymphoma, N Eng J Med 1994: 331:746-7].

when it is insufficient during injection: resistance to phagocytosis, induction of apoptosis and the like.

[PETERSON P.K., VERHOEF J., SCHMELING D. & QUIE P.G.: Kinetics of phagocytosis and bacterial killing by human polymorphonuclear leucocytes and monocytes, J. Infect. Dis. 136:502-509, 1977.

- 5 KIEHLBAUCH J.A., ALBACH R.A., BAUM I.K., CHANG K.P. Phagocytosis of *Campylobacter jejuni* and its intracellular survival in mononuclear phagocytes, Infect Immun 1985; 48:446-51].

**Constituents of the vaccine complex which is the subject
10 of the invention**

The complex of the invention comprises dual molecules constituted by the coupling of a functional amino acid arm, ensuring binding to a target, with a genetic RNA arm corresponding to the coded description of
15 the composition of the functional arm.

A - The RNAs of ribosomal origin which can be used may be extracted from the strains chosen from the following group, this list not being limitative:

- *Helicobacter pylori* (or *Campylobacter*),
20 *hepaticus*, *coronari* ...
- *Klebsiella pneumoniae*
- *Streptococcus* (*pneumoniae* and *pyrogenes*)
- *Staphylococcus aureus*
- *Serratia marcescens*
- 25 - *Escherichia coli*
- *Salmonella typhimurium*
- *Corynebacterium* (*granulosum*, *parvum*, *acnes*)
- *Mycobacterium* (*tuberculosis*, *smegmatis*, *chelonei*)
- *Hemophilus influenzae*

- *Pneumococcus* type II
- *Rothia dentocariosus*
- *Bacterium coli*
- *Shigella dysenteriae*
- 5 - *Enterococcus*
- *Nocardia* (*asteroides*, *brasiliensis*, *rhodocrans*,
 opaca, *rubra*)
- *Calmette-Guerin bacillus*,

or from a mixture thereof.

- 10 The average molecular weights of these RNAs are
between 5104 and 108 Dalton.

- Many industrial processes exist for the prepara-
tion of RNA. We will cite as an example the process for
extracting RNA described in *Infect. and Immunity*, 1. 574-
15 82. 1970; the bacteria are ground and then subjected to
fractional precipitation, the ribosomal proteins are
solubilized, the RNA precipitated is treated with Pronase
and, finally, purified by ion-exchange chromatography.

- If the RNA is obtained by enzymatic route, the
20 final purification may be carried out by molecular sieve
chromatography. See in particular on this subject:

- C. EHRESMAN (1972) - *Biochimie*, 54, 901
- H. KAGAWA (1972) - *J. Biochem.*, (1972), 827
- M. SANTER (1973) - *J. Bact.*, 116, 1304
- 25 - NOMURA (1974) - *Ribosomes* - Ed. Cold Spring
Harbor Laboratory.

B - The membrane fractions of bacterial cells
which can be used may be extracted from the following
strains, the lists given not being limitative:

09125747 082508

1 - for capsular polysaccharides

- a. *Helicobacter pylori* and *hepaticus*
- b. *Klebsiella pneumoniae*
- c. *Streptococcus pneumoniae*
- 5 d. *Haemophilus influenzae*
- e. *Escherichia coli*

a. *Helicobacter pylori*, *hepaticus* and *coronarii*

[HILLS B.A., Gastric mucosal barrier: evidence
for *Helicobacter pylori* ingesting gastric surfactant and
10 deriving protection from it. Gut. 1993 May; 34(5): 588-
93.

GENTA R.M., ROBASON GO, GRAHAM D.Y., Simultaneous
visualization of *Helicobacter pylori* and gastric
morphology; a new strain. Human Pathology; 1994 Mar: 25
15 (3); 221-6.

MAJEWSKI S.I., and C.S. GOODWIN, 1988,
Restriction endonuclease analysis of the genome of
Campylobacter pylori with a rapid extraction method:
evidence for considerable genomic variation. J. Infect.
20 Dis. 157; 465-471.

GEIS G., LEYING H., SUEBAUM S., MAI U. &
OPFERKUCH W.: Ultrastructure and chemical analysis of
Campylobacter pylori flagella. J. Clin. Microbiol, 27;
436-441, 1989].

25 b. *Klebsiella pneumoniae*

[C. ERBING, L. KENNE, B. LINBERG, J. LONNGREN
(1976) - Structural studies of the capsular poly-
saccharide of *Klebsiella pneumoniae* type I (Carbohydr.
Res., 50 (1976) 115-20).

W. NIMMICH (1968) Zur Isolierung und qualitativen Bausteinanalyse der K. Antigen von Klebsiellen [Isolation of the Klebsiella K antigen and qualitative analysis of its structural components] (Med. Mikrobio and Immunol., 154, 117, 131).

C. RICHARD (1973) - Etude antigenique et biochimique de 500 souches de Klebsiella [Antigenic and biochemical study of 500 Klebsiella strains] (Ann. Biol. Clin., 1973)].

10 c. Streptococcus pneumoniae:

[F. KAUFFMANN and E. LUND (1954) (Int. Bull. Bact. Nomencl. 4, 125-28).

FELTON and OTTINGER (J. of Bacteriology, 1942, 43, 94, 105)

15 M. COLIN, M.D. MAC LEOD et al., Prevention of pneumococcal pneumoniae by immunization with specific capsular polysaccharides (J. Exp. Med., 1945, 82, 445-65).

20 A.R. DOCHEZ and O.T. AVERY - The elaboration of specific soluble substance by Pneumococcus during growth (1971) (J. Exp. Med. 26, 477-93).

WEST PHAL and LUDERITZ (1952) (Z. Naturf. 7B, 148).

25 C.P.J. GLAUDEMANS and H.P. TREFFERS - An improved preparation of the capsular polysaccharide from Diplococcus pneumoniae (Carbohydr. Res. 1967, 4, 181-84)].

d. Hemophilus influenzae (capsular polysaccharide polyribosephosphate type)

[P. ANDERSON et al. (1972) - Immunization of humans with polyribosephosphate, the capsular antigen of *Hemophilus influenzae* type B (J. of Clin. Invest., vol. 51, 1972, 39-44).

- 5 P. ANDERSON et al. (1977) - Isolation of the capsular polysaccharide from supernatant of *Hemophilus influenzae* type B (Infect. and Immun., 1977, 15 (2), 472-77)].

e. *Escherichia coli* (capsular polysaccharides)

- 10 [LUDERITZ et al. (1977) - Somatic and capsular antigens of gram-negative bacteria (Compr. Biochem. 26 A, 105-228).

- BOYER H.W. and D. ROULLAND-DISSOIX, (1969) - A complementation analysis of the restriction and
15 modification in *Escherichia coli*, J. Mol. Biol. (41:459-472).

CASADABAN, M. and S. N. COHEN (1980) - Analysis of gene control signals by DNA fusion and cloning in *E. coli*, J. Mol. Biol. (138; 179-207).

- 20 LUGTENBERG B., J. Meijers, R. Peters, P van der Hock and L. van Alphen (1975) - Electrophoretic resolution of the "major outer membrane protein" of *Escherichia coli* K12 into four bands. (FEBS Lett. 58; 254-258)].

- 25 2 - For the membrane lipopolysaccharides (LPS) -
Corynebacterium (*avidum*, *bovis*, *diphtheriae*, *enzymicum*, *equi*, *fascians*, *flaccum*, *faciens*, *flavidum*, *fustiforme*, *granulosum*, *helvolum*, *hypertrophicans*, *insidiosum*, *liquefaciens*, *parvum*, *paurometabolum*, *pyogenes*,

0012747 082509
00220 442200

tumescens, xerosis)

- and the gram-negatives:
- *Helicobacter pylori*, *hepaticus*, *coronari*
 - *Klebsiella* (*pneumoniae* and *rhinoscleromatis*)
 - *Salmonella typhimurium*
 - *Serratia* (*marcescens*, *corralina*, *indica*, *plymuthica*, *kiluea*)
 - *Neisseria meningitidis*
 - *Escherichia coli*
- [GOODWIN C.S. "Helicobacter Pylori: 10th anniversary of its culture in April 1982". (Gut 1993; 34: 293-4).
- C. ERBIN et al. (1977) - Structural studies on the *Klebsiella* LPS (Carbohydr. Res., 56, 377-81).
- C.B. CASTOR et al. (1971) - Characteristics of a highly purified pyrogenic LPS of *Klebsiella pneumoniae* (J. of Pharm. Sci. 60, (10), 1578-80).
- K. FUKUSHI (1964) - Extraction and purification of endotoxin from Enterobacteriaceae: a comparison of selected methods and sources (J. of Bacteriol. 87, (2), 391-400).
- G. A. LIMJUCO - Studies on the chemical composition of LPS from *Neisseria meningitidis* group B (J. of Gen. Microbiol. 1978, 104, 187-91).
- G.A. ADAMS (1967) - Extraction of LPS from gram-negative bacteria with DMSO (Canad. J. Biochem., 45, 422-26).
- K.G. JOHNSON (1976) - Improved techniques for the preparation of bacterial LPS (Canad. J. Microbiol. (22),

29-34).

Y.B. KIM et al. (1967) - Biologically active endotoxins from *Salmonella mutans* (J. of Bacteriol., 94, (5), 1320-261)].

5 3 - For the membrane proteins

- *Helicobacter pylori*
- *Escherichia coli*
- *Serratia marcescens*
- *Streptococcus pyogenes*
- 10 - *Salmonella typhimurium*.

Helicobacter pylori, *Hepaticus*, *coronari*

GOBERT (B.), LABIGNE (A.), de KORWIN (J.D.), CONROY (M.C.), BENE (M.C.), FAURE (G.C.) - Polymerase chain reaction for *Helicobacter pylori*, (Rev. Esp. Enf 15 Digest, 1980, 78 (suppl 1), 4.

TOWBIN, H., T. STAHELIN and J. GORDON, 1979. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets; procedure and some applications. Proc. Natl. Acad. Sci. USA 76:4350-4354.

20 *Escherichia coli*

S.F. STIRM et al. (1967) - Episome, carried surface antigen K 88 of *Escherichia coli* (J. of Bacteriol., 93, (2), 731-39).

S.J. BETZ et al. (1977) - Chemical and biological 25 properties of a protein rich fraction of bacterial LPS (J. of Immunol., 119 (4), 1475-81).

Serratia marcescens

W. WOBER (1971) - Studies on the protein moiety of endotoxin from gram-negative bacteria,

0015747-08266

characterisation of the protein-moiety isolated by acetic acid hydrolysis of endotoxin of *Serratia marcescens*.

Streptococcus pyogenes

- M.K. WITTNER (1977) - Homologous and heterologous
5 protection of mice with group-A Streptococcal M protein vaccine (Infect. and Immun., 1977, 15, (1), 104-8).

Salmonella thyphimurium

- N. KUUSI et al. (1979) - Immunization with major
outer mebrane protein in experimental salmonellosis of
10 mice (Infect. and Immun., 1979, 25, (3), 857-62).

C. BARBER et al. (1972) - The protective role of
proteins from *Salmonella thyphimurium* in infection of
mice with their natural pathogen (Rev. Immunol., 36, 77-
81).

- 15 G. DELORD (1979) - Etude d'un antigène vaccinant
contenu dans le surnageant de culture de *Salmonella*
thyphimurium, souche M-206. [Study of a vaccinating
antigen contained in the culture supernatant of
Salmonella thyphimurium strain M-206] Medical thesis in
20 Lyon No. 428, 1979.

G.W. GOODMAN (1979) - Characterization of the
chemical and physical properties of a novel B-lymphocyte
activator endotoxin protein (Infect. and Immun., 1979,
24(3), 685-96).

- 25 4 - For the teichoic and lipoteichoic acids

Streptococci, *staphylococci* and *lactobacilli* (the
surface of gram-positive bacteria is made of teichoic
acid, which is a glycerol polymer, linked by
phosphodiester bridges).

The following articles describe the methods of production:

M.M. BURGER (1966) - Teichoic acids: antigenic determinants, chain separation and their location in the cell wall (Microbiology 56, 910-17).

K.W. KNOX (1973) - Immunological properties of teichoic acids (Bacteriol. Reviews, 37, 21, 215-57).

G.A. MILLER (1976) - Effects of streptococcal lipoteichoic acid on host response in mice (Infect. and Immun., 1976, 13, (5), 1408-17).

A.J. WICKEN et al. (1975) - Lipoteichoic acids: a new class of bacterial antigens (Science, 187, 1161-67).

Various assays possible

RNA

* FISKE and SUBBAROW - Assay of phosphorus. HPLC chromatography on an ion-exchange column for qualitative control (J. Biol. Chem. (1926), 66, 375).

Proteins

* LOWRY (J. Biol. Chem. (1951), 193, 265-75).

Hexoses

* T.A. SCOTT - Colorimetric assay using anthrone (Anal. Chem. (1953). 25, 1956-61).

Hexosamines

* L.A. ELSON (Biochem. J (1953), 27, 1824-28).

Lipopolysaccharides

* J. JANDA and E. WORK (Febs Letters, 1971, 16(4), 343-45).

C - The other immunity adjuvant factors, in addition to

the membrane fractions, are

- collagen type III
- sodium chloride

The collagen type III used is characterized by:

5 a - Amino acid sequences similar to the following
sequence (the concentrations are expressed in g/kg):

	- aspartic acid	AA	51.5
	- hydroxyproline	HP	107.0
	- threonine	TH	16.1
10	- serine	SE	27.8
	- glutamic acid	GA	95.9
	- proline	PR	124.0
	- glycine	GL	149.0
	- alanine	AL	87.9
15	- valine	VA	23.3
	- methionine	ME	7.5
	- isoleucine	IL	14.4
	- leucine	LE	27.8
	- tyrosine	TY	6.7
20	- phenylalanine	PA	14.4
	- lysine	LY	28.6
	- histidine	HI	5.5
	- arginine	AR	73.0

b - The following standard analysis:

25	- colour	yellowish white
	- apparent density	250 g/l
	- moisture	6%
	- pH of a 10% solution	6.9
	- Engler viscosity at 40°C	2.5

(17.75% solution)

- fat content 0.9%
- ash content 2.2%
- content of Fe + Cu + Ca 462 mg/kg
- 5 - heavy metals not detectable by arc emission spectrography
- elemental analysis C 46.80%
- H 7.10%
- N 14.96%

10 The composition of the vaccine complex which is
the subject of the invention, combining ribosomal RNAs or
RNA fragments, membrane fractions (for example proteo-
glycans from *Klebsiella pneumoniae*) and collagen type
15 III, supplemented with sodium chloride and an anti-
inflammatory agent, makes it possible, by administration
of low doses causing no toxicity, to obtain a high level
of protection and of cure.

The preferred presentation is the injectable form
of the composition presented above, but it is possible to
20 use other presentations and/or other areas or additives
compatible with a medical use.

Mechanism of action of the vaccine complex

This therapeutic (vaccine) complex may be assimilated to a specific vaccine (through an "inert system"
25 which is intended to increase the immunogenicity of a
recombinant subunit vaccine and of vaccines consisting of
peptides), and a nonspecific vaccine with the characteristics of a lymphokine, which, by attaching to the
macrophages, plays an essential role in the immune

response towards Helicobacter [KAZI J.I., SINNIH
R., JAFFRAY N.A., ALAM S.M., ZAMAN V., ZUBERI S.J. & KAZI
A.M.: Cellular and humoral immune response in
Campylobacter pylori-associated chronic gastritis,
5 J. Pathol. 159; 231-237, 1989].

Since 1974-75 (A.S. and G.P. YOUMANS), it has
been observed that the effect of inhibition of the immune
response to RNA was provided by various inhibitors.

YOUMANS had worked on a single bacterial strain
10 (Mycobacterium tuberculosis), whose "parasitism" is
solely intracellular.

VENNEMAN et al. have thought since 1972 that the
real antigen could be associated with RNA, whose role
could be that of an adjuvant. They vaccinated mice with
15 ribosomal RNA, extracted with phenol at 65°C from
ribosomes of a strain of Salmonella typhimurium. Thirty
days after this vaccination, it was found that the
animals were better protected than with an (attenuated)
live strain vaccine.

20 It was in particular observed that the level of
protection depended on the quantity of RNA injected.

For example: the ribosomal RNA extracted from
Streptococcus pneumoniae induces protection of a humoral
nature and the ribosomal RNA extracted from Klebsiella
25 pneumoniae induces protection of a cellular nature.

[TRIEU-CUOT, P., G. GERBAUD, T. LAMBERT and
P. COURVALIN (1985) - In vivo transfer of genetic infor-
mation between gram-positive and gram-negative bacteria.
(EMBO J. 4:3583-3587)].

00125747-082500

This mixture, when injected in vivo into mice and guinea pigs, exerts an action on the alveolar macrophages.

This "transient" effect is determined by assaying
5 the acid phosphatase in the direct haemolysis plaques in contact with mouse spleen cells.

The treatment with our therapeutic and vaccine complex is, for its part, followed by a cellular and humoral immunostimulant effect, with a significant
10 specific and nonspecific action on *Helicobacter pylori*. It is the patient's own body which is stirred into action to "reject the infected cells". A cure is obtained by the action of the PMNs (Polymorphonuclear leukocytes) and of the monocytes simultaneously stirred into action.

15 [ANDERSEN L.P.; NIELSEN H. Survival and ultrastructural changes of *Helicobacter pylori* after phagocytosis by human polymorphonuclear leukocytes and monocytes, APMIS; 1993 Jan.: 101(1); 61-72]

[STEIGBIGEL R.T., LAMBERT L. H. & REMINGTON J.S.;
20 Phagocytic and bactericidal properties of normal human monocytes, J. Clin. Invest. 53; 131-142, 1974]

[YAM L.T., Li C.Y. & CROSBY W.H.; Cytochemical identification of monocytes and granulocytes, Am. J. Clin. Pathol. 55; 283-290, 1971].

25 This therapeutic mechanism therefore makes it possible to produce a natural cloning by virtue of the (nonspecific bacterial ribosomal) RNAs opsonized by the adjuvant developed (combination of membrane proteoglycans, of collagen type III and of sodium chloride).

This cloning induces vaccination against the idiotypes of the antibodies, as well as the production of antibodies against the site for attachment of the bacteria. To reduce or inhibit the inflammatory reaction,
5 it is necessary to use, during treatments with the vaccine complex, corticoids (Betamethasone type, for example) in the form of disodium phosphate, at a dose of 20 to 60 mg, by the I.V. or I.M. route.

This action is also accompanied by production of
10 endogenous interferon as well as an activation of the NK cells.

The aim of our immunomodulatory vaccine complex is therefore to induce a local and general immune response which has the effect of preventing or at least
15 of reducing (down to a possible self-defence threshold) the proliferation of an infectious agent introduced into the body.

- PRUUL H., LEE P.C., GOODWIN C.S. & MACDONALD P.J. - Interaction of Campylobacter pyloridis with human
20 immune defence mechanisms, (J. Med. Microbiol. 23; 233-238, 1987).

- RATHBONE B.J., WYATT J.I., WORSLEY B.W., SHIRES S.E., TREJDOSIEWICZ L.K., HEATLEY R.V. & LOSOWSKY M.S.
- Systemic and local antibody response to gastric
25 Campylobacter pyloridis in non-ulcer dyspepsia, (Gut. 27; 642-647, 1986).

- STACEY A.R., HAWTIN P.R. & NEWELL D.G. -Local immune responses to Helicobacter pylori injections. In: Malgerthheimer P. & Ditschuneit H. (Eds.): Helicobacter

pylori, Gastritis and Peptic Ulcer, (Springer Verlag, Berlin-Heidelberg, 1990, pp. 162-166).

Our therapeutic innovation consists, inter alia, in moderating or eliminating the existence of "suppressive cells" exerting a proinfectious action, in causing an anti-ulcerous reaction by a defensive cellular and/or humoral response; it is the therapeutic response to the problem detected since 1993 by Kist et al.

[KIST M; SPIEGELHALDER C.; MORIKI T.; SCHAEFER H.E. - Interaction of *Helicobacter pylori* (strain 151) and *Campylobacter coli* with human peripheral polymorphonuclear granulocytes], and in preventing infectious recidivations:

- BORODY T., ANDREWS P., MANCUSO N., JANKIEWICZ E., BRANDL S. - *Helicobacter pylori* reinfection 4 years post-eradication; (Lancet 1992, 339-1295).

- BELL G.D., POWELL K.U., BURRIDGE S.M., HARRISON G., RAMEH B., WEIL J. et al. - Reinfection or recrudescence after apparently successful eradication of *Helicobacter pylori* infection: Implications for treatment of patients with duodenal ulcer disease, (Q.J. Med 1993, 86; 375-382).

In conclusion, our therapeutic complex acts by directed evolution, producing RNA molecules which block the *Helicobacter pylori* infection and increase the immunodefence.

[SUERBAUM S., C. JOSENHANS, and A. LABIGNE (1993) - Cloning and genetic characterization of the *Helicobacter pylori* and *Helicobacter mustelae* flaB flagellin

genes and construction of *H. pylori* flaA- and flaB-negative mutants by electroporation-mediated allelic exchange. (J. Bacteriol. 175:3278-3288).

- HAAS R., T.F. MEYER, and J.P. VAN PUTTEN (1993)

- 5 - Aflagellated mutants of *Helicobacter pylori* generated by genetic transformation of naturally competent strains using transposon shuttle mutagenesis. (Mol. Microbiol. 8:753-760)

- CHEN M., LEE A., HAZELL S., HU P., LI Y. -

- 10 Protective immunisation against *Helicobacter*: the need for stimulation of common mucosal immune system (abstract). (Gastroenterology 1993, 104 (suppl): A681)].

- It was, moreover, observed during the various clinical trials which were carried out, that the complex of the invention could be successfully substituted for conventional treatments, using in particular triple therapy, in notorious cases of bacterial resistance.
- 15

Techniques for administering the vaccine complex

- The vaccine complex may be administered orally or parenterally:
- 20

- * either by direct intravenous injection
- * or by slow infusion
- * or by subcutaneous injection
- * or by the transdermal route (per 24 h)

- 25 These various techniques have been tried successfully.

The daily doses and their frequency depend largely on the patient's condition. There is no risk of an overdose given the non-toxicity of the complex.

By the intravenous route sequences of one week per month may be used, each day of the week of treatment comprising a slow infusion of 500 ml of a solution containing:

- 5 - 0.9% sodium chloride
- 40 µg of membrane saccharide fractions
(Klebsiella pneumoniae proteoglycans)
- 30 µg of (ribosomal) RNA from:
- * Helicobacter pylori 7 µg
- 10 * Diplococcus pneumoniae 7 µg
- * Streptococcus pyogenes (A 12) 7 µg
- * Klebsiella pneumoniae 7 µg
- * Hemophilus influenzae 2 µg
- 10 µg of collagen type III described above
- 15 - 8 mg of Betamethasone disodium phosphate (that
is to say 2 ml of injectable solution).
- This treatment by slow I.V. infusion may be
replaced by a treatment by subcutaneous injections on
patients who can be followed on an ambulatory basis, each
- 20 injection containing:
- 40 µg of membrane saccharide fractions
(Klebsiella pneumoniae proteoglycans)
- 30 µg of (ribosomal) RNA from:
- * Helicobacter pylori 7 µg
- 25 * Diplococcus pneumoniae 7 µg
- * Streptococcus pyogenes (A 12) 7 µg
- * Klebsiella pneumoniae 7 µg
- * Hemophilus influenzae 2 µg
- 10 µg of collagen type III described above

00125747-002569

- 0.5 ml of sodium chloride at 0.9%

- 4 mg of Betamethasone disodium phosphate (that is to say 1 ml of injectable solution).

This treatment may be continued for several
5 weeks.

By the oral route:

* using tablets,

2 tablets per day, in a single dose in the morning on an empty stomach, each tablet containing:

10 - 400 µg of membrane saccharide fractions
(Klebsiella pneumoniae proteoglycans)

- 300 µg of (ribosomal) RNA from:

	* Helicobacter pylori	70 µg
	* Diplococcus pneumoniae	70 µg
15	* Streptococcus pyogenes (A 12)	70 µg
	* Klebsiella pneumoniae	70 µg
	* Hemophilus influenzae	20 µg

- 100 µg of collagen type III described above

- 2 mg of Betamethasone disodium phosphate.

20 This treatment can be provided at the rate of 2 tablets per day for one month, followed by booster periods of two tablets per day, one week per month for 3 months.

By the transdermal route

Adhesive transdermal therapeutic sytem composed
25 of a reservoir and a permeable membrane providing continuous passage of the active ingredients across the skin and into the bloodstream at a constant rate.

The device should be stuck to a healthy skin

surface which is dry and not very hairy (side wall of the abdomen or of the thorax for example).

It comprises:

- adhesive polymer
- 5 - carrier for the adhesive: polyethylene
- silicone polyester protective filter

Its content is the content of one tablet, and its dosage is identical to the oral route (at the rate of one "patch" for 2 daily tablets).

10 The following non-limiting examples are given to illustrate the concrete results for our therapeutic vaccine complex.

Example 1

Mr. Robert G., 64 years old, was hospitalized
15 following epigastralgia, pyrosis and abdominal pain associated with a transit disorder with alternating diarrhoea - constipation. Digestive endoscopy showed a gastrooesophageal reflux pathology by the opening of the cardia, causing an oesophagitis and a peptic ulcer of the
20 lower oesophagus.

Biopsies were performed, as well as a rapid urease test. The latter, as well as anatomopathology and culture, confirmed the presence of *Helicobacter pylori*.

Conventional treatment (antisecretory and two
25 antibiotics) was prescribed. The tritherapy did not lead to a clinical cure.

Six weeks after the end of the treatment, verification of eradication by the ¹³C-labelled urea breath test led to conclusion on the proliferation of bacteria

because of its positive nature.

The treatment with the vaccine complex which is the subject of the invention was then carried out in the form of subcutaneous injections.

5 A month later, clinical cure was observed and the carbon-13-labelled urea breath test was negative.

Six months later, another verification by the ¹³C-labelled urea breath test and a verification endoscopy showed an established cure.

10 For one year, the cure has been definitive.

Example 2

Mr. Serge Y., 48 years old, had a type B antral gastritis. Treatment with immunomodulatory complex (the only previous treatments were gastric dressings) in IV
15 form. Clinical cure was obtained fifteen days after the therapeutic sequence. The verifications (¹³C-labelled urea breath test) have been negative for one year.

Example 3

Mr. Pierre K. had a duodenal ulcer confirmed by
20 endoscopy (+biopsy, urease test, ELISA tests).

Treatment by the oral route was then introduced. Three weeks later, clinical cure was obtained.

Six weeks later, verification by the ¹³C-labelled urea breath test confirmed the eradication.

25 Six months later, no recidivation was recorded, and the Elisa test showed a nonsignificant (< 50%) antibody level.

Example 4

Mrs. Sarah L. had a duodenal ulcer associated

with a type B gastritis.

The presence of gastric cancer was detected among her brothers and sisters. A full check-up was carried out to show the positive nature of all the tests by an
5 invasive method: culture, histology, amplification of the viral genome (PCR), urea test.

Treatment by the intravenous route over one week and then by subcutaneous boosters over six months was then introduced.

10 Given the high familial risk, an endoscopy with biopsy was performed from the third month: PCR, cytology, culture, CLO test, were negative.

At the sixth month, a breath test (^{13}C) confirmed clinical cure.

CLAIMS

1. Specific therapeutic immunomodulatory complex,
characterized in that it comprises:
 - dual molecules constituted by the coupling of a functional amino acid arm, ensuring binding to a target, with a genetic RNA arm corresponding to the coded description of the composition of the functional arm,
 - bacterial membrane fractions glycopeptides and/or lipopolysaccharides,
- 10 the ribonucleic acids (RNA) being of ribosomal origin and extracted from strains chosen from the following group: *Helicobacter pylori*, *hepaticus*, *coronari*, *Campylobacter* or from a mixture thereof.
2. Immunomodulatory complex according to Claim 1,
15 **characterized in that** the amino acids are amino acids from collagen.
3. Immunomodulatory complex according to Claim 2,
characterized in that the amino acids from collagen are chosen from the following group: aspartic acid,
20 hydroxyproline, threonine, serine, glutamic acid, proline, glycine, alanine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, lysine, histidine, arginine, or a mixture thereof.
4. Immunomodulatory complex according to one of
25 Claims 1 to 3, for its use in the treatment of diseases caused by *Helicobacter* bacteria, by the production of antibodies and the production of endogenous interferon.
5. Immunomodulatory complex according to one of

Claims 1 to 3, for its use as an anti-idiotypic vaccine against the idiotypes of anti-bacterial antibodies which make it possible to avoid, in particular, recidivations of the initial digestive tract pathology.

5 6. Immunomodulatory complex according to one of Claims 1 to 3, for its use against bacterial resistance to conventional antibiotic treatments and the like.

7. Anti-Helicobacter-specific immunomodulatory and vaccine complex according to one of the preceding claims,
10 **characterized in that it** is presented in a packaging allowing the simultaneous administration of major anti-inflammatory agents of the corticoid type, of anti-biotics, of antisecretory agents, (proton pump inhibitors, of the type including Omeprazole or anti-H2,
15 and the like) or other products with bacteriostatic, bactericidal or bacteriolytic effects, for eradicating Helicobacter generating pathogeneses by factors linked to the bacterium (production of various cytotoxins, of inflammation mediators: Interleukin I, tumour necrosis
20 factor alpha), or by factors linked to the host.

8. Immunomodulatory complex according to the preceding claim, **characterized by** a packaging in the form such that it can be administered by various routes: infusions, intravenous injections, subcutaneous injections, trans-
25 dermal devices, or per os.

PLEASE NOTE:
YOU MUST
COMPLETE THE
FOLLOWING:

COMBINED DECLARATION AND POWER OF ATTORNEY
FOR PATENT AND DESIGN APPLICATIONS

ATTORNEY DOCKET NO.
TORO 0101 PUS

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:*

Insert Title

Anti-Helicobacter vaccine complex

Check Box If
Appropriate -
For Use Without
Specification
Attached

the specification of which is attached hereto unless the following box is checked:

☐ was filed on _____ as United
States Application Number _____ or
PCT International Application Number _____
and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

Insert Priority
Information
(if appropriate)

96 02445	FRANCE	02/25/1997	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More Than 12 Months (6 Months for Designs) Prior To The Filing Date of This Application:

Country

Application No.

Date of Filing (Month/Day/Year)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Number)

(Filing Date)

(Status — patented, pending, abandoned)

(Application Number)

(Filing Date)

(Status — patented, pending, abandoned)

*NOTE: Must be completed.

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

John A. Artz, Reg. No. 25,824; John S. Artz, Reg. No. 36,431;
Kevin G. Mierzwa, Reg. No. 38,049; Robert P. Renke, Reg. No. 40,783

PLEASE NOTE:
YOU MUST
COMPLETE THE
FOLLOWING:

Send Correspondence to:

John A. Artz
LYON & ARTZ, PLC
28333 Telegraph Road, Suite 250
Southfield, MI 48034

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole
Inventor:
Insert Name of Inventor
Insert Date This
Document Is Signed
Insert Residence
Insert Citizenship

Insert Post Office
Address

Full Name of Second
Inventor, if any:

see above

Full Name of Third
Inventor, if any:

see above

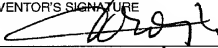
Full Name of Fourth
Inventor, if any:

see above

Full Name of Fifth
Inventor, if any:

see above

*Note: Must be completed
— date this document is
signed.

GIVEN NAME <u>Fernand Narbey</u>	FAMILY NAME <u>TOROSSIAN</u>	INVENTOR'S SIGNATURE 	DATE* July 17, 1997
Residence (City, State & Country) <u>TOULOUSE, France</u>		CITIZENSHIP French	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country) <u>10 rue Noë1 Ballay, 31400 TOULOUSE, France</u>			
GIVEN NAME		FAMILY NAME	INVENTOR'S SIGNATURE
Residence (City, State & Country)		CITIZENSHIP	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			
GIVEN NAME		FAMILY NAME	INVENTOR'S SIGNATURE
Residence (City, State & Country)		CITIZENSHIP	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			
GIVEN NAME		FAMILY NAME	INVENTOR'S SIGNATURE
Residence (City, State & Country)		CITIZENSHIP	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			
GIVEN NAME		FAMILY NAME	INVENTOR'S SIGNATURE
Residence (City, State & Country)		CITIZENSHIP	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			
GIVEN NAME		FAMILY NAME	INVENTOR'S SIGNATURE
Residence (City, State & Country)		CITIZENSHIP	
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			